REMARKS/ARGUMENTS

Claims 1-3, 8-11, 13-14, and 16 are active in this application.

Claim 1 recites:

> A multilayer dosage form comprising
> a) a neutral core,
> b) an inner methacrylate copolymer coating comprising at least 90% by weight of (meth)acrylate monomers having neutral radicals, wherein the methacrylate copolymer has a minimum film-forming temperature as specified in DIN 53 787 not exceeding 30°C, and a pharmaceutically active substance bound to the methacrylate polymer, wherein the inner coating does not comprise plasticizer; and
> c) an outer coating which comprises a (meth)acrylate copolymer which is composed of 10 to 30% by weight methyl methacrylate, 50 to 70% by weight methyl acrylate and 5 to 15% by weight methacrylic acid,
> wherein the values for the percentage release of active substance in a hypotonic and an isotonic release medium based on phosphate buffer pH 6.8 do not differ from one another at any time in the period from 1 to 5 hours by more than 10%.

As discussed in the application in the paragraph bridging pages 5-6, this formulation provided initial slow release (due to the outer layer) followed by a similar slow release of the active that was not affected by the ionic strength of the dissolution medium. More specifically, in the Examples of this application it is demonstrated that when a pharmaceutically active substance is bound to the methacrylate polymer of the inner coat, the release was not affected by the ionic coat. In other words, the unexpected effect that is observed in the application (and to which Applicants previously referred) is not a function of the outer coating but the inner coating with active bound thereto. The outer coatings modify the start of release as is shown in Example 4 (using Eudragit® FS30D for delivery to the colon) and Example 5 (using Eudragit® L30D for delivery to the intestine).

Starting on page 26, Examples 1-3 embeded budesonide (active) in Eudragit® NE 30D (the inner coat methacrylate polymer). As explained in the application on page 31, FIG.

2 shows the comparative release profiles of Example 1 in isotonic and hypotonic conditions. Example 1 has no outer coating.

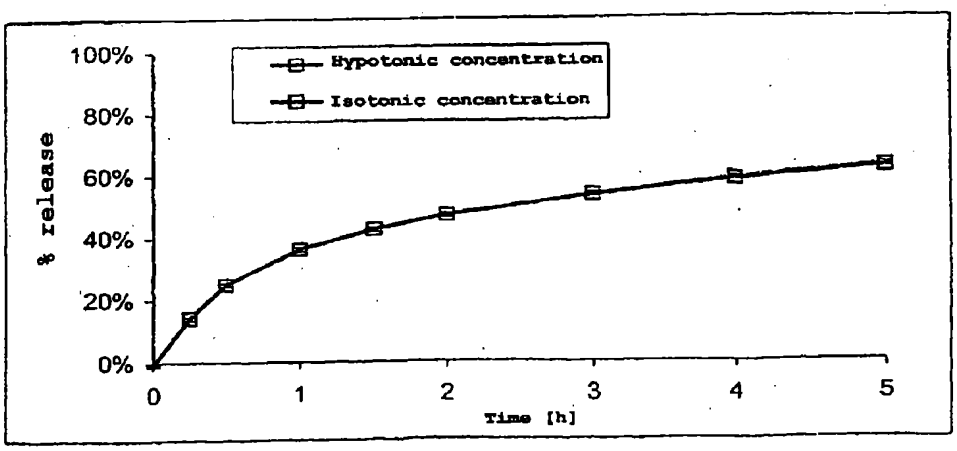

Fig. 2

Example 5, adds the outer coating of Eudragit L30D-55 as a gastroresistant coating. As explained on page 33, FIG. 5 shows the comparative release profile of the formulation with Eudragit® NE30D with budenoside bound thereto and the outer, gastroresistant coating.

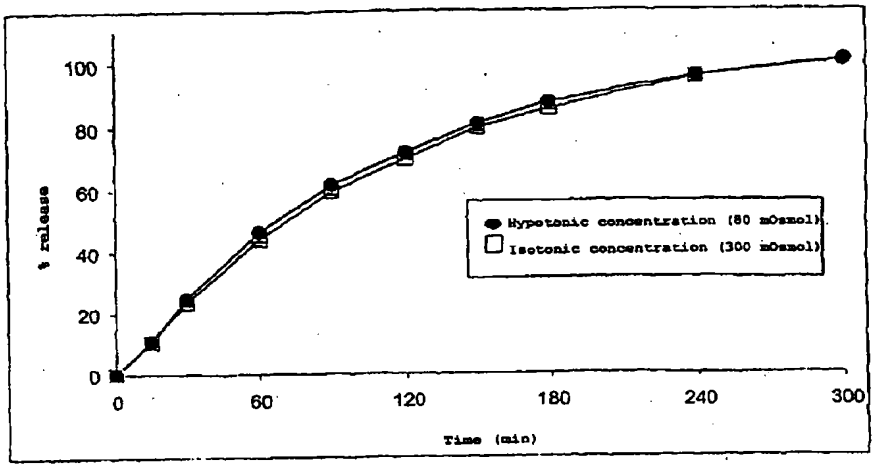

Fig. 5

These results show that the release of the active from the pellet is unaffected by the osmotic conditions in the release medium. Again, referencing Example 1 and FIG. 2 above, the conclusion that is drawn from these experiments is that the inner methacrylate polymer, e.g., Eudragit® NE30D was responsible for this unexpected effect.

Example 6, uses the same outer, gastro-resistant coating (Eudragit® L30 D-55) as in Example 5 but instead of a methacrylate polymer within the defined parameters of the claims (e.g., Eudragit® NE30D), Example 6 uses Eudragit® Rl 30D (not within the defined parameters in the claims). As shown in the Table on page 34, the inner coating included only this RL30D material, the remaining ingredients are for the outer gastro-resistant coating. The results of this experiment are shown in FIG. 6.

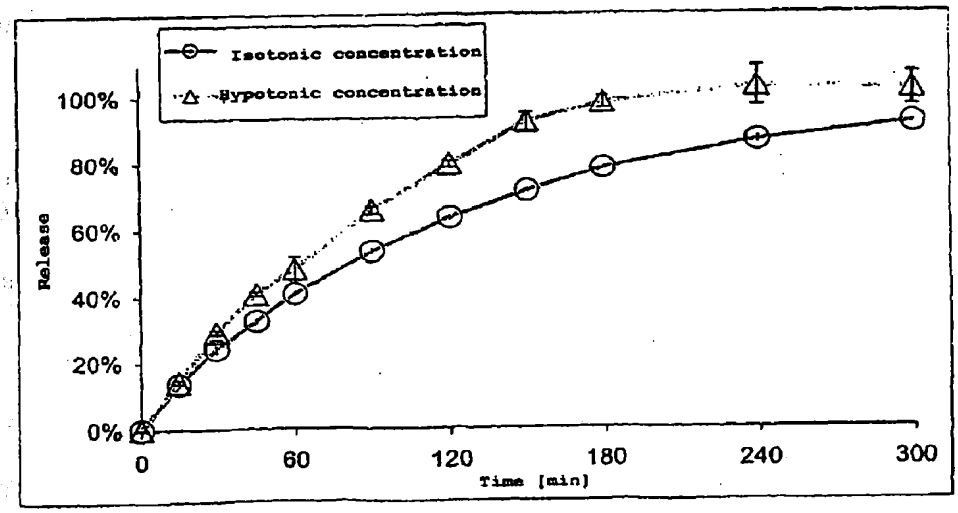

Fig. 6

These results show that the replacement of Eudragit® NE30D with Eudragit® RL30D as the inner coat to which the active is bound had differential release depending on the osmotic conditions of the release medium. Taken together, Examples 1, 5 and 6 as well as FIGs 2, 5 and 6 demonstrate that the inner methacrylate polymer, e.g., Eudragit® NE30D was responsible for this unexpected effect.

In the Office Action, the Examiner has maintained the rejection in view of Ulmius (US 5,643,602) with or without Beckert et al (WO 01/68058). The reasons underlying the rejection remain largely the same as before.

Ulmius describes a multilayer drug delivery unit (see col. 5, lines 3-26) including any number of polymers, including Eudragit®-type polymers (see also the Examples). Col. 5 of Ulmius describes a first layer including many different types of polymers, including Eudragit® type polymers but none of the Examples in Ulmius describe polymers in the inner coat (or layer) that includes a polymer like that which is claimed). While the Examples use some of those Eudragit® polymers as the outer layer, the Examiner has determined that it would have been obvious to use any one of the Eudragit® polymers as an inner (or first) layer replacing the ethylcellulose (Aquacoat ECD30 is an aqueous dispersion of ethylcellulose[1]) as actually used by Ulmius. Beckert is cited for further evidence of actives and additional disclosure pertaining to multi-layer drug forms (see page 8 of the Official Action mailed April 16, 2008).

First, there is nothing in Ulmius which provides the necessary direction to specifically select the type of methacrylate polymer as the inner coat to which the active is bound as defined in the claims from amongst all the possible polymers that are described by Ulmius (see listing in col. 5, for example). Second, that the selection of the specific methacrylate polymer permitted release of the active that was not affected by the ionic strength of the dissolution medium (see Examples in the application and the discussion above) could not have been predicted based on what Ulmius described (see page 5, last ¶ of the present application).

The rejection was maintained in large part as it was determined that Applicants have not provided sufficient evidence to demonstrate an unexpected effect, in

[1] See, e.g., www.fmcbiopolymer.com/pharmaceutical/Products/Aquacoat.

terms of the osmotic conditions that had been explained previously. However, as detailed above, referencing the specification, Applicants have, in fact, presented such evidence. These results presented in the specification show that the replacement of Eudragit® NE30D with Eudragit® RL30D as the inner coat to which the active is bound had differential release depending on the osmotic conditions of the release medium. Taken together, Examples 1, 5 and 6 as well as FIGs 2, 5 and 6 demonstrate that the inner methacrylate polymer, e.g., Eudragit® NE30D was responsible for this unexpected effect.

Also, on page 5 of the Official Action, the Examiner noted that there were differences between the formulations of Examples 5 and 6 that may have contributed to the effect observed by the Applicants and to which Applicants have relied upon in rebutting the obviousness rejection previously. As should be apparent from the above-discussion, the effect that was observed was the result of the selection of specific type of methacrylate polymer as the inner coating with the active bound thereto. The differences in the outer-coating are for the purpose of delaying release until a certain point in the gastrointestinal track but, again referencing FIG. 2 the effect was one due to the inner coating.

As explained in MPEP 2145: "An "obvious to try" rationale may support a conclusion that a claim would have been obvious where one skilled in the art is choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success. " [A] person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely that product [was] not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740, 82 USPQ2d 1385, 1397 (2007).

However, as the evidence of record (in the specification) shows, reasonable prediction of success from the teachings of cited art are not present for the percentage release of active

substance as defined in Claim 1 because the evidence shows that combinations within the teachings of Ulmius (see Example 6 of the present specification using an RL 30D inner coating) lead to compositions not meeting that definition. See also, *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd,* 533 F.3d 1353, 87 U.S.P.Q.2D 1452 (Fed. Cir. 2008): "To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable."

As is clear from the figures, when the composition as defined in the claims was tested, the release profile remained relatively unchanged in the different ionic conditions, which was not the case for the composition in Example 6. Such an effect could not have been predicted based on what Ulmius described (see page 5, last ¶ of the present application).

Still further, with respect to claims 13-16, the selection of the specific methacrylate polymer enabled the active to be provided in the inner coating without the aid of excipients such as plasticizers or release agents as is typically the case in such formulations (see pages 4-5 in the specification citing to WO 01/68767, also the cited art. This is not at all suggested by Ulmius and/or Beckert.

As the basis of the rejection is *prima facie* reasonable predictability and the evidence shows that this is not the case, it has not been established that the claims are obvious in view of the cited reference.

In addition to their showing that there is no *prima facie* case, Applicants have shown an unexpected improvement in terms of the hypotonic/isotonic robust dissolution behavior. While Applicants do not concede that a skilled person would chose Eudragit® NE for the inner matrix from Ulmius and combine it with the outer Eudragit® FS coating of Beckert but even if that combination was appropriate, one skilled in the art would never expect the "hypotonic/isotonic" effect as has been so clearly demonstrated for the claimed invention.

There is nothing in Ulmius and Beckert which provides the necessary direction to specifically select the type of methacrylate polymer defined in the claims from amongst all the possible polymers that are described by Ulmius (see listing in col. 5, for example). Second, that the selection of the specific methacrylate polymer permitted slow release of the active that was not affected by the ionic strength of the dissolution medium (see Examples in the application) could not have been predicted based on what Ulmius described (see page 5, last ¶ of the present application).

Withdrawal of the rejection is requested.

The Examiner has also raised a new rejection combining Beckert with Gang. The basis of the rejection, stated on pages 7-8 of the Official Action is that Ulmius does not disclose the combination of Eudragit® NE30D with Eudragit® FS, and therefore relies on Gang.

Gang teaches a colon delivery system employing an NE 30D inter coating and a FS outer coating. *Gang et al.* use the active ingredient (theophylline) placed in the pellet core and not bound in the inner methacrylate copolymer coating layer as claimed. This results in time dependent release curves (*s. Gang, Fig.1*) which are different from the release curves of the present invention. Time dependent means that at the same pH the different examples of *Gang et al.* start the release of the theophylline, depending on the coating thickness of the inner EUDRAGIT® NE layer, at different times but then in the same fast manner (delayed pulsed release).

In contrast to this the release of the active ingredient (e.g., budesonide) in the present application is triggered either by the proportions of EUDRAGIT® NE/budesonide (Fig. 1) and, most important, as a function of the pH (Fig. 3) and not as a function of time. Thus, the

claimed invention and *Gang et al.* differ in the position of the active ingredient within the pellet and also remarkably in the kind of release curves.

Further, as already established in the discussion pertaining to the Ulmius and Beckert rejection above,

As is clear from the figures, when the composition as defined in the claims was tested, the release profile remained relatively unchanged in the different ionic conditions, which was not the case for the composition in Example 6. Such an effect could not have been predicted based on what Ulmius and/or Gang described (see page 5, last ¶ of the present application).

As the basis of the rejection is *prima facie* reasonable predictability and the evidence shows that this is not the case, it has not been established that the claims are obvious in view of the cited reference.

In addition to their showing that there is no *prima facie* case, Applicants have shown an unexpected improvement in terms of the hypotonic/isotonic robust dissolution behavior. While Applicants do not concede that a skilled person would chose Eudragit® NE for the inner matrix from Ulmius and combine it with the outer Eudragit® FS coating of Gang but even if that combination was appropriate, one skilled in the art would never expect the "hypotonic/isotonic" effect as has been so clearly demonstrated for the claimed invention.

There is nothing in Ulmius and Gang which provides the necessary direction to specifically select the type of methacrylate polymer defined in the claims from amongst all the possible polymers that are described by Ulmius (see listing in col. 5, for example). Second, that the selection of the specific methacrylate polymer permitted slow release of the active that was not affected by the ionic strength of the dissolution medium (see Examples in the application) could not have been predicted based on what Ulmius and/or Gang described (see page 5, last ¶ of the present application).

Withdrawal of the rejection is requested.

A Notice of Allowance is also requested.

Respectfully submitted,

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